

Review article

Possible integration of artificial intelligence with photodynamic therapy and diagnosis: A review

Nkune Williams Nkune, Heidi Abrahamse*

Laser Research Centre, Faculty of Health Sciences, University of Johannesburg, P.O. Box 17011, Doornfontein, 2028, South Africa

ARTICLE INFO

Keywords:

Photodynamic therapy
 photodynamic diagnosis
 artificial intelligence
 Cancer therapy

ABSTRACT

Cancer remains a deadly disease with a low median survival rate. The increase in cancer mortality rates is attributed to limitations in diagnosis, prognosis prediction, and therapeutic interventions. Photodynamic diagnosis (PDD) and photodynamic therapy (PDT) are promising light-based systems used for the diagnosis and treatment of cancer. They incorporate photosensitisers (PSs), light and oxygen to visualize or eradicate cancer cells. Even though nanotechnology has advanced these techniques, several limitations, such as target selectivity, PS dose, prognosis, poor light delivery, and inaccurate diagnosis, have hampered their overall efficiency. Artificial intelligence (AI) is a branch of computer science that focusses on predictions and automation, playing a pivotal role in expediting drug discovery and promoting precision in healthcare. AI algorithms have the potential to optimise the design of PSs for improved tissue penetration and affinity, enhancing target-selectivity via identification of novel biomarkers and therapeutic targets, and optimising light delivery parameters for uniform light propagation in tissues. Therefore, this review highlights advancements in the integration of AI in PDD and PDT applications over the last decade, as well as a new perspective on how AI technology can improve PDD and PDT and continue to improve human health in the future.

1. Introduction

Cancer has been considered a dreadful public health, societal and economic concern in recent years, accounting for millions of deaths globally [1]. The current treatment alternatives for cancer treatment entail surgery, chemotherapy, hormone therapy, radiation therapy, immunotherapy and targeted therapy [2,3]. Although some of these current therapies have shown remarkable cytostasis and antitumour effects, they are often accompanied by unwanted side effects and a high chance of recurrences [4]. Surgery may result in local metastases, while radiation therapy and chemotherapy are associated with side effects such as hair loss, bone marrow suppression, fatigue, nausea and vomiting [5]. Despite the recent advances in oncology, the poor cancer prognosis is attributed to its detection in advanced stages and uncertainties in diagnostic precision, resulting in low survival rates in cancer patients [6]. The sole dependence on distinct tumour characteristics renders traditional methods such as magnetic resonance imaging, biopsy and ultrasound ineffective for the initial cancer diagnosis [6]. These challenges inspired the development of novel techniques such as photodynamic therapy (PDT) and photodynamic photodiagnosis

(PDD). PDT is a promising modality for treating various cancers through programmed cell death, apoptosis, or necrosis of tumour cells [7]. The success of PDT relies on the integration of three fundamentals: a photosensitiser (PS), a suitable wavelength of light and oxygen. Initially, PDT is executed by exposing the PS to an appropriate wavelength of light. Subsequently, the activated PS transfers its energy to generate reactive oxygen species (ROS). Ultimately, ROS destroys cancer cells via either apoptotic or necrotic cell death mechanisms [8]. PDD is based on the excitation of administered PS, which has preferentially accumulated in tumorous tissues over normal cells. When the targeted tumour region is exposed to light of a specific wavelength, fluorescent signals are emitted and detected to help locate the tumour [9].

Despite accruing evidence showing the effectiveness of PDT and PDD, there are still major issues that need to be addressed. Hence, researchers are actively engaged in integrating photosensitisers with nanotechnology to increase their bioavailability in tumours with minimal off-target localization and toxicity. It is well proven that nano-based therapies address the most formidable challenges in cancer therapy such as tumour metastasis and drug resistance. The incorporation of nano-based systems with PDT allows for coordinated drug release, efficient

* Corresponding author.

E-mail addresses: 217078898@student.uj.ac.za (N.W. Nkune), habrahamse@uj.ac.za (H. Abrahamse).<https://doi.org/10.1016/j.jddst.2024.106210>

Received 3 July 2024; Received in revised form 5 September 2024; Accepted 15 September 2024

Available online 16 September 2024

1773-2247/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

light absorption and the ability evade hypoxia-induced resistance. Furthermore, the development of PS nanocarrier systems increases ROS yield and the overall PDT efficacy [10]. The advancements in biology, medicine and nanotechnology have led to a rapid shift in cancer treatment towards a personalised and data-intensive approach. To enhance therapeutic outcomes and decrease off-target toxicity, patients' characteristics must be closely examined, and the therapeutic drug or combinatorial approach should be globally optimised from the onset of design. In this regard, to guarantee accuracy of cancer diagnosis and treatment, artificial intelligence (AI) and recent innovations have been extensively used to analyse multiple-source and multiple-dimensional data [11–13].

Several lines of evidence state that AI-mediated techniques hold great promise in medicine and life science applications, such as for early detection of pandemic disease outbreaks, radiological and histological diagnosis, and multi-omics investigations for identifying molecular profiles [14,15]. Typically, the design of nanoparticle-based drugs is intricate because factors like multi-modal mechanisms of action and the execution of their synergistic therapeutic effects need to be highly considered [16]. Thus, it is imperative to assess the physical and chemical properties, biocompatibility, pharmacokinetics and possible interactions between loaded drugs and their nanocarrier systems [17]. The interactions between nanodrugs and cancer cells, including cellular uptake, responses elicited in the tumour microenvironment, intracellular distribution and therapeutic effects also need to be taken into consideration to enhance the efficacy and safety of nanodrugs [18,19]. Although the integration of AI and nanotechnology is still in its early stages, AI can be extremely important in these processes. Recent studies by Alexeree et al. evaluated the efficacy and safety profile of novel phthalocyanine-gold nanoconjugates (Pc-Au NCs) as nanocarrier systems for *in vivo* PDT. Alexeree and colleagues developed a non-invasive biospeckle optical imaging technique to quantitatively visualize alterations in the internal dynamics of biological tissue induced by PDT. Secondly, Alexeree et al. used laser-induced breakdown spectroscopy (LIBS) to determine the localization of gold nanoparticles (AuNPs) within the healthy and cancerous tissue, which revealed the biocompatibility and phototoxic effects of the Pc-Au NCs. Thereafter, the biospeckle images and LIBS spectra were captured from tumour and normal tissues of male BALB/c xenograft models before and after PDT, which were then statistically treated using AI techniques. The results proved that biospeckle and LIBS statistical properties hold great promise in determining the efficacy of the Pc-Au NCs as a PS nanocarrier system for *in vivo* PDT [8].

Pharmaceutical formulations can be optimised to improve the transport and targeting of nanomedicines by using AI algorithms to model drug release kinetics from nanocarriers, estimate drug encapsulation efficiency, and predict interactions between nanocarriers and their incorporated drugs, biological mediators, or cell membranes. The use of AI algorithms to predict the interactions of nanocarriers and their encapsulated drugs, biological barriers, or cell membranes, estimate drug loading efficiency, and coordinate drug release kinetics from nanocarriers can optimise nanopharmaceutical formulations to improve nanomedicine delivery and targeting. AI-mediated techniques can also identify drug combinations and optimise combinatorial drug approaches to promote drug synergism while reducing off-target toxicity, ultimately enhancing clinical outcomes. Furthermore, AI combined with nanoscale biosensors can aid in the discovery of distinct cancer biomarkers and therapeutic targets to facilitate active target drug delivery [20].

Uniform light distribution is indispensable for efficient PDT and PDD, as uneven light exposure can result in suboptimal treatment outcomes. The distribution of treatment light is influenced by tissue geometry and optics [21,22]. Therefore, uneven illumination can cause incomplete excitation of the PS, resulting in inadequate therapeutic effects or an indefinite diagnosis. AI algorithms provides highly accurate predictive models for optimising light delivery and light distribution patterns within tumour tissues [23]. Machine learning techniques can

modify light source parameters in real-time to ascertain the coverage of the targeted tumour regions while minimising unwanted side effects on adjacent normal tissues. This can yield reproducible and improved treatment outcomes [24]. The intricate relationship between light, photosensitiser, and oxygen makes dosimetry complicated. Accurate dosimetry is critical for delivering appropriate light fluency to targeted tissue regions. Dosimetry can be influenced by tissue complexity, interactions of light such as absorption, scattering or reflections [21]. In view of this, AI can adjust dosimetry by means of an automated system that analyses the interactions between the light and tissue in real time [25]. Kim et al. developed an AI-enabled, implantable, multichannel wireless telemetry for PDT to overcome low levels of tissue penetration and PS excitation. Kim and colleagues established DeepLabCut (DLC)-informed low-power wireless telemetry with an integrated thermal/light simulation. The simulator incorporated optimised wavelengths and light sources, and DLC-assisted wireless telemetry utilised the parameters from the simulator to allow for sufficient irradiation of tumours through high-throughput (<20 mice) and multi-wavelength operation. Kim et al. reported that Hypericin and Foscan significantly inhibited tumour growth in cancer xenograft models after irradiation, which merits further investigation in research and clinical trials [26].

Furthermore, AI can also be used to develop *in vitro* three-dimensional (3-D) culture models that mimic human physiology responses to therapeutics and have the ability to capture both the efficacy of a drug and potential toxicity to healthy organs. Studies by Shahi et al. investigated the effect of gelatinous spongy scaffold containing nano-hydroxyapatite on the induction of odontogenic activity of dental pulp stem cells. Shahi and colleagues noted an increase in the survival and differentiation rates of dental pulp stem cells (DPSCs) grown in the scaffold, suggesting that the scaffold exerted favourable effects on odontogenic activity, which holds promise for future application in endodontic rejuvenation [27]. Moreover, recent studies have developed nanobiomaterials/bioinks-based scaffolds in 3-D bioprinting for tissue engineering and artificial human organs. Printed structures have been extensively employed in tissue engineering to heal or repair impaired tissues or organs, as well as *in vitro* tissue modelling to screen and validate new drugs before moving to clinical trials, offering a conducive environment for cell development closely resembling its native surroundings [28]. Furthermore, by incorporating nanotechnology into 3-D printed configurations, it might be possible to manipulate these structures in response to a variety of external physical stimuli, offering a further tool for use in medical applications [28,29].

The review explores the possible integration of AI systems with PDD and PDT to address their existing challenges, such as off-target toxicity, complex PS optimisation delivery, ununiform light distribution and therapy resistance, to enhance their effectiveness in cancer treatment and diagnosis.

2. The principle of photodynamic therapy (PDT) and photodynamic diagnosis (PDD)

The principle of PDT hinges on the presence of light with an appropriate wavelength, molecular oxygen, and photoactivatable PS, which yield cytotoxic ROS used to annihilate various oncological and non-oncological diseases [30]. When exposed to light, the PS molecule (single state) gets activated and transitions to an excited singlet state. During this process, some of the energy is emitted as fluorescence and the PS transitions to the excited triplet state. The remaining energy is further released in two ways. In a type I reaction, energy is transferred into adjacent biomolecules either as electrons or hydrogen, which results in the formation of free and anion radicals of the PS and the substrate [10]. The electron interacts with oxygen molecules, generating superoxide anion radicals and ultimately ROS, which destroy cancer cells via oxidative stress. In type II reaction, the excited triplet PS state reacts directly with molecular oxygen, converting it into a highly oxidizing singlet oxygen. The aforementioned reactions can occur at the

same time competitively. The generated ROS and singlet oxygen species cause protein denaturation and lipid and other organelle disruption within at the tumour site, eventually inducing apoptotic, necrotic, or autophagic cell death mechanisms [30].

The principle behind PDD involves three steps: (a) PS retention at target tumour tissues; (b) illumination of the area of interest with a short wavelength (330–400 nm); and (c) capturing fluorescent signals emitted by the previously administered PS. When exposure to light, the PS gets activated and transitions from the ground state to an excited singlet state [9] PS excited electrons go through “internal conversion,” in which their electronic energy is replaced by vibrational energy, allowing them to release gained energy in the form of fluorescence, which aids diagnosis. In principle, the excited PS singlet state is short-lived (a few nanoseconds) and thus cannot initiate cellular mechanisms that trigger cell signalling death pathways and so only allows for effective diagnostic visualization without cellular destruction [9]. Fig. 1 illustrated the mechanism of action behind PDD and PDT applications.

2.1. Photosensitisers for photodynamic therapy

PSs are natural or synthetic photoactive compounds crucial for PDT applications. These compounds can absorb light with a particular wavelength, which in turn evokes a cascade of photochemical or photophysical reactions [31]. Virtually all PSs used in cancer treatment are characterised by a tetrapyrrole structure, closely resembling the protoporphyrin found in haemoglobin. In a clinical setting, a PS of choice is: (1) harmless until photoactivated; (2) water-compatible for ease of systemic application; (3) activated by light at a wavelength between 400 and 600 nm to prevent photosensitivity; (4) stable at room temperature; and (5) and (6) quickly cleared from the patient [31]. Haematoporphyrin derivative (HPD), a first-generation photosensitiser was made of various monomers coupled with dimers and polymers of haematoporphyrin [32]. Photofrin sodium, a product sold commercially under the brand name Photofrin, has gained popularity in PDT applications. Its clinical application is, however, limited by a number of factors, such as poor tissue penetration depth to its maximum absorption at a shorter wavelength of 630 nm, or poor chemical purity (it is composed of more than 600 molecules). In addition, after PDT, this PS causes skin hypersensitivity due to its high retention in the skin and slow clearance from the body. The disadvantages of the first-generation PSs compelled

scientist to investigate new photoactive compounds, which led to the discovery of second-generation PSs [33,34].

Second-generation PSs comprise pure and well-characterised photoactive molecules such as chlorines, porphyrin derivatives, phthalocyanines, and naphthalocyanines. These PSs demonstrate efficient singlet oxygen yield, and a prominent absorption peak within the therapeutic window (650–800 nm). Furthermore, they have a strong affinity for cancer cells and relatively rapid elimination from the body, thereby reducing unwanted side effects on normal cells [34]. Despite several advantages of second-generation PS, they are inherently insoluble in water, which considerably hampers their intravenous administration and calls for development of novel drug delivery methods [35].

2.2. Photosensitisers for tumour diagnosis

Photodynamic diagnosis (PDD) exploits the fluorescence emitted by PSs to identify a tumorous region *in situ* [31]. In PDD, a PS shows high affinity for targeted tumour tissues relative to normal tissues. The PS is then photoactivated upon exposure to a light source at a specific wavelength to elicit diagnostic fluorescent signals in tumour regions [36]. PDD can be converted into PDT by increasing the light dose or prolonging the photoirradiation duration [31]. Moreover, PDD is considered to be an integral part of image guided surgery, specifically fluorescent guided resection [37]. PDD ALA has been widely used in PDD applications due to its ability to distinguish cancerous tissues from normal tissues [38]. Studies by Hefti et al., 2010 reported that 5-aminolevulinic acid (5-ALA) fluorescence microscopy hold great promise for specific biological tumour marker for malignant glioma resection [39]. Therefore, it may help in differentiating cancerous tissue from normal brain tissue. Research conducted by Stummer and colleagues reported that the administration of 5-ALA induced tumour fluorescence, leading to a greater resection of contrast-enhancing tumours and an improved prognosis in patients with malignant gliomas [40].

In other studies, PDD showed greater detection of bladder tumours in patients, especially those diagnosed with carcinoma *in situ*, when compared to white-light cystoscopy [41]. Kausch and colleagues concluded that a complete resection and longer recurrence-free survival rates were achieved in patients diagnosed with PDD [41]. Likewise, Mowatt et al. proved PDD superiority over white-light cystoscopy in the detection of bladder tumours [42]. PDD-mediated ALA led to a more

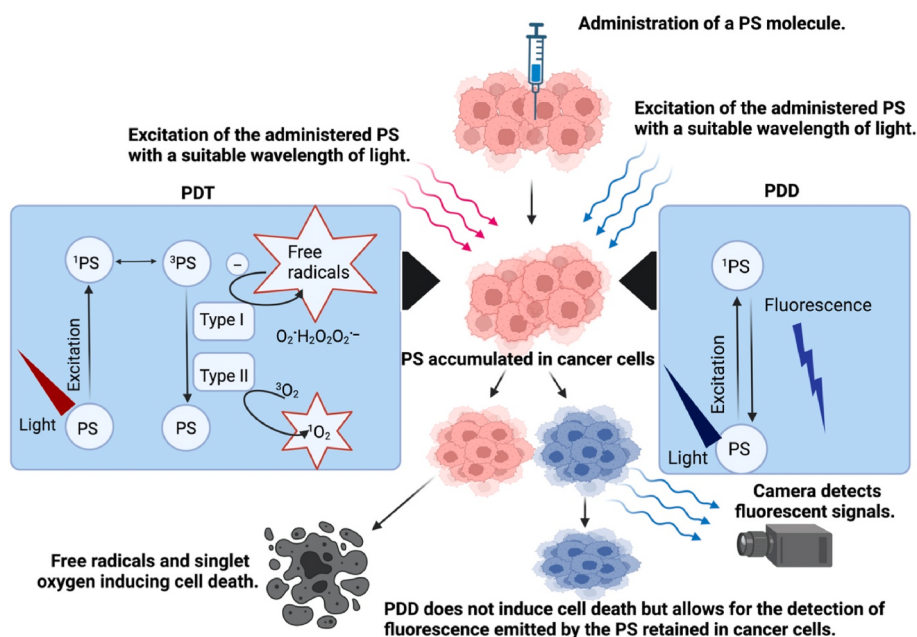


Fig. 1. PDT and PDD mechanisms of action.

complete transurethral resection of the bladder tumour and improved the patient survival rate [42]. Turan and colleagues designed a molecular demultiplexer system that can automatically attenuate singlet oxygen production and simultaneously initiate a bright emission when apoptosis is triggered [43]. This innovative molecular automaton addresses the confinement of undesirable damage by excessive singlet oxygen generation. Cancer is typically diagnosed in the advanced stages, necessitating the development of novel diagnostic methods for early detection of a tumour and enhancing patients survival rates [44]. In this regard, the integration of PDD and PDT is promising approach for the diagnosis and eradication of cancer. Therefore, multifunctional near-infrared fluorescence photoactive agents are likely to pave new avenues for targeted tumour imaging for the diagnosis and treatment of cancer [45].

3. Drawbacks of photodynamic therapy and photodynamic diagnosis

The longstanding obstacle to PDT and PDD is the poor tumour distribution that traditional PSs show after being administered, which lowers the PS's bioavailability in the targeted tumour regions. Insufficient retention of active molecules in tumorous regions can lead to both incomplete tumour destruction and an inaccurate diagnosis [46]. Moreover, undesirable biodistribution may promote prolonged periods of off-target accumulation in normal tissues. To tackle these challenges, significant efforts have been made to enhance the distribution of PSs to improve the efficacy of PDT and PDD, as well as reduce off-target accumulation. In recent years, various smart delivery systems, such as targeting moieties, liposomes, and nanocarriers, have relatively provided solutions for poor biodistribution [9,10,46]. However, for decades, accurate light delivery has been an indispensable fundamental for PDT and PDD applications. Numerous clinical PDT trials fail due to issues related to insufficient delivery of light doses to tumorous regions or excessive delivery of light, thereby causing unwanted side effects [21, 36,47]. Dosimetry promotes a homogenous or non-homogenous dose distribution in targeted tumour regions and also determines the quantitative optimal dosing of healthy neighbouring tissues. Ideally, the light dose should only cover the malignant region, with negligible effect on normal regions [48].

The penetration of light is influenced by the optical properties of the tissue and the wavelength of the light. Tissues are complex in nature, and their inhomogeneous organelles (e.g., nuclei, membranes, etc.) result in light scattering, reflection, or absorption [49,50]. In addition, endogenous chromophores, such as haemoglobin, can absorb visible light at shorter wavelengths, whereas water can absorb light at longer wavelengths, thereby limiting the efficacy of PDT. This capped the range of wavelengths from 600 nm to 1300 nm for optimal tissue penetration. However, light beyond 850 nm is inadequate to excite the PS to its triplet, for it yields singlet oxygen in PDT applications. In this regard, the "therapeutic window" of most PDT applications falls in the red region of the spectrum between 620 and 850 nm to achieve optimal tissue penetration and PS excitation [49].

There are currently no real-time dosimetry systems, and this has led to clinicians predicting parameters for PS dose and light intensity to be administered at the tissue interface, which have rarely yielded appreciable light distribution in any patient [48]. In larger mass tissues, predicting light fluence within the tissue remains a daunting challenge because it requires precise measurements of tissue absorption, scatter, and anisotropy parameters, as well as analytic or computational systems to determine the light fluence [47]. Therefore, without definite dosimetry, it is difficult to distinguish failures related to either an inadequate amount of PS, light, or oxygen [48]. Excessive treatment causes side effects, while subpar treatment leads to failure. This dosimetry uncertainty and the clinician's lack of knowledge about its implications will delay promising PSs from realising their full potential. Therefore, there is a dire need for real-time dosimetry systems to offer the most

convenient and accurate approach to estimating the light dose required by the surface of a tissue [21,47,48].

4. The role of nanotechnology in photodynamic therapy and photodynamic diagnosis enhancement

Nanotechnology is a fast-growing field of science and technology that focuses on the study of structures and components that are at the nanometre scale (1–100 nm) and the utilisation of these nanomaterials for practical applications. Nanomedicine is a novel interdisciplinary field that implements the principles and protocols of nanotechnology in medical research and clinical settings to allow for precise diagnosis and treatment of ailments with intricate pathogenesis at the molecular level [51]. In recent years, nanoparticle-based nanocarrier systems have shown great potential to enhance cancer diagnosis and treatment via smart PS delivery systems [52]. This is attributed to the fact that nanoparticles (NPs) are small but possess a larger surface area-to-volume ratio, allowing the loading of PSs for improved bioavailability in targeted tumour tissue. This is attributed to the fact that nanoparticles (NPs) are small in size but possess a larger surface area-to-volume ratio, allowing the loading of PSs for improved bioavailability in targeted tumour tissue [53].

The integration of NPs with PSs not only enhances the stability, targeting selectivity, and water compatibility of PSs but also reduces their undesirable dark and off-targeted toxicity. Furthermore, the modification of PSs with NPs protects them from being eliminated by immune system barriers by simulating biological molecules and thereby evading premature clearance, which improves PS *in vivo* circulation and cellular uptake loads [54]. In addition, since NPs have small dimensions, they can easily penetrate cells and predominantly exhibit high affinity for tumour cells via the passive enhanced permeability and retention (EPR) uptake effect. The EPR phenomenon is attributed to the larger pore size of neo-vasculatures and impaired lymphatic clearance of tumours, and it is greatly influenced by tiny molecules such as NPs, thereby reducing overall cytotoxicity in normal tissues [55]. However, various factors can influence the EPR effect-mediated retention of the PS in targeted tumour regions, such as the nanocarrier size, shape and surface properties [56]. Therefore, it is very imperative to optimise nanocarrier systems to yield better therapeutic outcomes [56]. In recent years, significant efforts have been dedicated to increasing the targeted delivery of PSs by encapsulating them into NPs further modified with targeting molecules correlating with receptors expressed by tumour cells [57].

5. Nanocarrier systems and third-generation photosensitisers for photodynamic therapy and photodynamic diagnosis applications

Over the past few years, great strides have been made in the diagnosis and treatment of cancer. This has led to the development of third-generation PS, which encompasses second-generation PS modified with NPs alone or with targeting moieties to facilitate either passive or active-targeted PS delivery in cancer cells Fig. 2. Various organic and inorganic NPs such as have been widely used in PDD and PDT advantages due to their distinct advantages (Table 1) [46].

6. Nanocarrier systems for enhanced passive PS delivery in photodynamic diagnosis and therapy applications

Nanocarrier systems can serve as excellent PS delivery platforms since they not only improve cellular uptake in cancer cells but also confer stability, target-selectivity, and coordinate PS release while reducing unwanted toxicity in healthy tissues [67]. Various studies have been conducted to test the efficiency of PSs combined with NPs in PDT applications (Table 2). However, there are currently no studies for PDD passive nanocarrier platforms, which warrants further investigations.

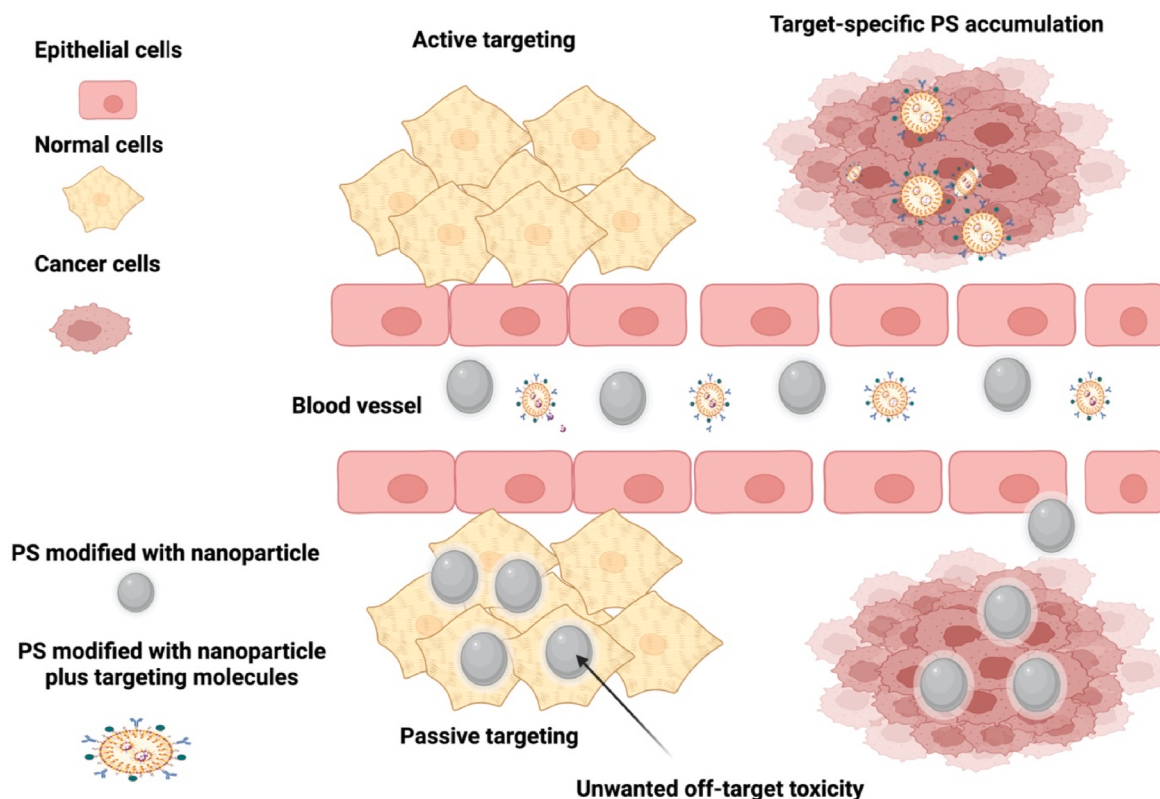


Fig. 2. Active targeting versus passive targeting. PS modified with nanoparticles shows unwanted off-target accumulation in normal cells, while PS modified with nanoparticles plus targeting biomolecules shows a selective affinity for cancer cells.

Despite several advantages exhibited by passive PS nanocarrier platforms, studies have indicated that the latter cannot exclusively distinguish normal tissues from tumour tissues and thus, to some extent, cause unwanted off-target toxicity. This concern prompted the development of active targeting nanocarrier platforms, which involve modifying PS-NP with targeting biomolecules that have a high affinity for cancer cells compared to healthy tissues [53].

7. Nanocarrier systems for enhanced active PS delivery in photodynamic diagnosis and therapy applications

In an effort to address limitations related to poor drug localization and unwanted collateral damage in cancer therapy, researchers are exploring nanocarrier systems further modified with specific targeting ligands (such as folic acid, small ligands, peptides, antibodies, or carbohydrates) to improve targeted accumulation [76]. When compared to passive targeting, active-targeting nanocarriers allow the PS to selectively accumulate in tumour cells, thereby increasing its bioavailability in tumour cells while sparing healthy tissues [53]. Table 3 summarises current studies that have further functionalised passive PS delivery systems with targeting moieties to enhance PDT outcomes in cancer therapy. However, since PDD is in its infancy, there is relatively little data as far as active PS nanocarrier systems are concerned. Recent studies by Simelane and colleagues noted that an active PS carry nanocarrier system showed an exclusive affinity for colon cancer cells versus normal human fibroblast cells in both PDD and PDT applications [52]. However, one of the daunting challenges associated [77] with active targeting platforms is the fact that they are strongly dependent on the size, surface chemistry, and target-specificity of the nanocarrier, as well as its disintegration and PS release kinetics once actively absorbed exclusively by targeted cells [78].

8. The role artificial intelligence in cancer diagnosis and treatment

Artificial intelligence (AI) has garnered significant attention in biomedical cancer research as it has provided a breakthrough in cancer diagnosis, therapy, and overall patient quality of life via innovative solutions. AI can help in the development of new remedies and treatment modalities, improve early detection of cancer via image analysis, and create customised treatment plans aligned with patient information [86]. Machine learning (ML) has revolutionised AI due to its ability to offer a multitude of algorithms that can improve identification or prediction accuracy with copious amounts of high-quality data. Deep learning (DL) is a branch of machine learning that relies on neural network models to overcome limitations faced by conventional machine learning [86,87].

Given that the human mind can only process small amounts of data quickly, AI has gained popularity in recent years as a novel approach for extremely intelligent decision-making. Cancer is a multifaceted disease characterised by countless genetic and epigenetic variations. Therefore, AI-based techniques have great potential to pave new avenues for the early identification of genetic mutations and aberrant protein interactions [88]. Modern biomedical research strives to introduce AI technology into clinical settings in a safe and ethical manner. AI-based assistance to pathologists and clinicians could be a significant step forward in predicting disease risk, diagnosis, prognosis, and therapy [86, 88]. In light of this, scientists can actually work together and share knowledge digitally, potentially speeding up disease diagnosis and new drug discovery [88].

8.1. Artificial intelligence-medical imaging

AI has revolutionised medical imaging technology, and it hinges on computational devices and bioinformatics-derived algorithms. It can

Table 1

Summarises widely used NPs photodynamic diagnosis and therapy. Applications.

NPs	ADVANTAGES	REFERENCE
ORGANIC		
Liposomes NPs	Easy to synthesis, can accommodate both hydrophilic and hydrophobic agents, coordinate drug release, biocompatible, versatile structure, low risk of eliciting immune reactions and highly stable	[58]
Carbon nanotubes	Biocompatibility, chemical stability, superior optical properties, controlled drug release, deep tissue penetration, and adaptable surface chemistry.	[59]
Dendrimers	Can deliver numerous therapies, has accurate structural control, avoids enzymatic degradation, is easy to customise, is water and biocompatible, and can transport hydrophobic anticancer drugs.	[60]
Micelle/polymeric NPs	Ease of synthesis, customisable properties, fewer side effects, resistance to enzymatic degradation, ability to encapsulate hydrophobic therapeutics, biocompatible and have a high loading capacity.	[61]
INORGANIC		
Gold NPs (AuNP)	Outstanding stability, adaptability, biocompatibility, prolonged therapeutic release, improved light absorption, photothermal cell death, and ease of synthesis.	[62]
Upconversion NPs	Durable stability, low toxicity in the dark, negligible oxygen dependence, and biocompatibility and biodegradability	[63]
Quantum dots	Photochemical stability, multiplexing, adjustable optical properties, appropriate for therapeutic and diagnostic uses, and efficient light emission.	[61]
Silica NPs	Has highly adjustable surface chemistry, excellent biocompatibility, high stability, and the capacity to mimic biological molecules. It can also bind to hydrophobic and hydrophilic agents with ease.	[64]
Ceramic NPs	High surface area, remarkable optical properties, low photobleaching, can evade degradation by biological barriers, chemically and thermally stable, tunable properties, biocompatible, multiple delivery of therapeutic drugs and demonstrate theranostic properties.	[65]
Magnetic NPs	Prolonged retention in tumour cells, modifiable surface properties, controlled drug release, enable real time monitoring, allow for multifunctional activities, improved penetration abilities and promote target-specificity of anticancer agents.	[66]

detect any erratic cellular growth and biological alterations in the body [89]. Medical images obtained with computed tomography (CT), a radiological technique, can capture the anatomical structure of a patient in both volumetric and morphological detail. A modern CT scanner can provide an extremely high-resolution scan of a patient, covering their entire body from head to toe [90]. Another commonly used medical imaging technology is magnetic resonance imaging (MRI), which has the ability to differentiate soft tissues, allowing for a clear examination of the interior of joints and ligaments. On the other hand, MRI can be used to identify cancer cells and capture images of almost any part of the body if there are differences in the density of soft tissues that can be recorded [91]. Additionally, DL algorithms and neural networks are used in the brain segmentation process. In combination, they provide a semi-automated method for classifying brain MRI scans into tumour regions and healthy tissue [92].

In recent years, breast cancer incidence has been on the rise, and its diagnosis mainly relies on ultrasonography. Improving the segmentation of breast ultrasonography images into functional tissues can determine

Table 2

Passive PS nanocarrier system used in PDT treatment of cancer.

Photosensitiser	Nanoparticle	Outcomes	Ref.
Zinc phthalocyanine (ZnPc)	Poly-ε-caprolactone (PCL) NPs	The conjugation of ZnPc to the PCL NPs not only improved the stability of the PS by also increased its cytotoxic effects by 90 % in vitro. The study concluded that PS nanocarrier systems have great potential in improving the outcomes of PDT.	[68]
Hypocrellin B	Nano silver loaded polymeric NPs	The nanocarrier system demonstrated a significant increase in the singlet oxygen yield and significantly induced 82.2 % cell death.	[69]
Indocyanine green (ICG)	Chitosan-coated liposomes	The encapsulation of ICGG in NPs enhanced the PS uptake by 2 fold in cancer cells	[70]
Protoporphyrin IX (PpIX)	Poly (lactic acid-glycolic acid) (PLGA)	PLGA significantly enhanced the photodamaging effect of PpIX, resulting in 80 % reduction in cells viability.	[71]
5-Aminolevulinic acid	Chitosan nanoparticles (NPs)	The nanoconjugate should a significant phototoxicity and improved intracellular accumulation	[72]
5,10,15,20-Tetrakis (2,4-dihydroxyphenyl) porphyrin (POR)	Silver nanoparticles (AgNPs)	AgNPs improved the cellular uptake of PS in cancer cells and exhibited increased ROS yield.	[73]
Chlorin e6	Gold nanoparticles (AuNPs)	AuNPs improved the singlet oxygen production of PS, which significantly improved in vitro and in vivo tumour cell death.	[74]
Pheophorbide a	Chitosan nanoparticles (NPs)	Pheophorbide-a conjugated to chitosan NPs, showed enhanced cellular uptake and increased therapeutic efficacy in tumour-bearing mice compared to free PS.	[75]

cancer location, evaluate the effectiveness of treatment, and calculate breast density. However, radiologists are compelled to segment patients manually, which is cumbersome and requires a high level of skill. Automated segmentation of ultrasound holds great promise for surmounting these challenges. A recent study demonstrated that fatty tissue, mass, fibro-glandular tissue, and skin can all be reliably classified from 3D images using convolutional neural network (CNN)-based segmentation. This discovery may pave new avenues for clinical breast cancer diagnosis in the future [93].

8.2. Integration of artificial intelligence with conventional cancer treatments

8.2.1. Radiotherapy

The implementation of AI in radiotherapy has shown tremendous potential in radiation oncology. AI technologies improve the precision and efficacy of cancer therapy. In radiotherapy, AI aims to identify tumours and organs at risk, facilitating proper treatment strategizing [94]. This improves the target-specificity of radiation therapy for tumorous tissues while minimising unwanted side effects in healthy tissues. AI-derived algorithms can effectively process large amounts of patient data and medical images, which facilitates treatment optimisation [95]. Furthermore, AI helps with real-time treatment monitoring, enabling timely modifications to the therapy plan per a patient's response [96].

Table 3
Active PS nanocarrier systems in photodynamic treatment of cancer.

Photosensitiser	Active nanocarrier	Outcomes	Refs
Ferrous chlorophyllin (Fe-CHL)	Poly (lactic acid-glycolic acid) (PLGA)-peptide	Fe-CHL active targeting enhanced bioavailability and ROS yields in cancer cells. Targeted PDT exhibited enhanced PS cellular uptake and increased ROS production in B16-F10 cells.	[79]
Chlorin e6 (Ce6)	Gold nanoparticles (AuNPs) modified with Epidermal Growth Factor (EGF)	The nanobioconjugate showed a considerable phototoxicity of 86 %, with no effect on normal cells. Further analysis revealed 58 % and 38 % necrotic and apoptotic cells, respectively, and 9-fold higher ROS levels in cancer cells versus normal cells.	[80]
Zinc phthalocyanine	Gold nanoparticles functionalised with Peptide-Lactose	Showed increased cellular uptake and superior ROS generation.	[81]
Pyropheophorbide	Perfluorocarbons (PFCs) modified with hyaluronic acid (HA)	The nanoconjugate exhibited an increased singlet oxygen yield, which reduced cell viability by 70 % and tumour mass.	[82]
Hypocrellin B	Hyaluronic acid bound to ceramide NPs and Paclitaxel anticancer agent	PDT combination therapy improved the cytotoxicity in cancer cells and tumour-bearing mice by inducing 90 % effective apoptotic cell death upon exposure to a 630 nm laser with a fluence of 16 J/cm ² .	[83]
Methylene blue	Polyacrylamide plus Peptide	Showed improved targeting abilities with improved phototoxicity in dose-dependent manner & irradiation time	[84]
Chlorin e6 (Ce6)	Silk-based NPs functionalised by cRGDFK	PDT significantly reduced tumour mass with remarkable biocompatibility and safety <i>in vivo</i> .	[85]

The application of AI in radiation therapy not only improves its overall efficacy but also allow for more customised and effective cancer management. The ongoing research and application of AI technology open up new opportunities for further enhancements in radiation oncology [94].

8.2.2. Immunotherapy

Significant efforts have been made to study tumour immunity and its resonance with the multifaceted microenvironment. Cancer immunotherapy is practically becoming the mainstay treatment option apart from traditional therapy and surgery for certain types of cancer [97,98]. The main objective of immunotherapy is to stimulate patients' autologous immunogenic immunity to fight tumour cells by eliciting immunogenic cell death [99,100]. Multiple physiological events are intricately regulated during this process, including tumour antigen presentation, activation of effector T cells, tumour-infiltration of T cells, and T cell-mediated tumour cell eradication [101,102]. However, it remains a challenge for clinicians to predict patients susceptibility to immunotherapy and prognosis. The application of AI can bolster immunotherapy by characterising immunological features presented by

cancer patients and predicting treatment outcomes in a non-invasive manner, thus guiding clinicians to strategize immunotherapy for cancer patients [103].

8.2.3. Chemotherapy

The application of AI is making significant progress in biomedical cancer research, especially in chemotherapy [104]. AI is essential in improving and personalising chemotherapy regimens for cancer patients. Several AI-based technologies have been widely employed to forecast the drug dosage, drug tolerance, and post-treatment survival rates of patients diagnosed with different cancer types [103]. Recent studies have employed ML tools to predict the effect of first-line oxaliplatin, a chemotherapeutic drug, on advanced colorectal cancer by distinguishing a 67-gene signature [105]. Through evaluating large datasets, AI helps oncologists design personalised treatment regimens based on each patient's distinct genetic and molecular profile, maximising therapeutic efficacy and reducing adverse effects. The incorporation of AI with chemotherapy not only increases the treatment efficacy but also reduces the invasive nature of chemotherapeutics, which immensely contributes to the ongoing progress in cancer research [106].

8.2.4. Targeted therapy

AI has also gained a great deal of attention in targeted therapy to offer tools that can improve its accuracy and therapeutic efficacy in cancer patients [104]. Through the analysis of multifaceted datasets and unique features presented by patients, physicians can adjust therapies in line with the characteristics of each patient's cancer, enabling more individualised and targeted treatments [106]. This strategy can enhance treatment outcomes, reduce adverse effects, and advance the field of biomedical cancer research [107]. It may also guide researchers towards the identification of precise molecular targets for therapeutic interventions. This will facilitate the development of individualised, efficacious treatment plans for individual patients and open up new fronts in the battle against cancer [108].

8.2.5. Surgery

Surgeons take years to hone their skills, and they must perform hundreds of operations to learn new techniques and incorporate them into their daily practices. However, human cognitive capabilities have limitations. In this instance, AI holds promise for processing high complexity and vast amounts of data in seconds for predictive analytics to improve the precision of decision-making processes [109]. However, as the medical AI community navigates the intricate ethical, technological, and human-centred challenges necessary for safe and adequate translation, implementing medical AI systems in routine trauma and emergency surgery care presents a crucial but largely unrealized opportunity. Skilled surgeons are understandably wary of euphoric, cutting-edge solutions that lack academic rigour and proof of superior performance in clinical settings. Even if AI technology predicts clinical outcomes with high accuracy hours or days in advance, its usage in trauma and emergency surgery will only be minimal until its deployment establishes confidence in the model's accuracy and lack of bias, tackles risk-sensitive decisions, and integrates with clinical workflows [110].

8.3. Integration of artificial intelligence with non-conventional photodynamic diagnosis and therapy

AI can significantly enhance drug delivery outcomes by modifying formulation design. The performance and efficacy of the drug delivery system are influenced by drug stability, solubility and release kinetics [111]. AI algorithms can suggest the best formulation techniques by examining data on the physicochemical properties cancer agents and excipients as well as their interactions. In this regard, AI can determine apt excipients or nanocarriers that enhance drug solubility, stability or release kinetics [112]. Additionally, it can identify cutting-edge

strategies of drug delivery that improve tissue penetration and drug target-specificity, such as lipid-mediated systems or nanoformulations. This information can be very essential for formulation purposes, thereby allowing for optimal drug delivery and improved therapeutic efficacy [113]. Furthermore, AI enables customised drug delivery based on the patient characteristics, such as genetics, demographics, and disease properties. This enables customised formulations to minimise adverse effects and maximise therapeutic efficacy. Drug delivery strategies can be tuned for specific drugs and patient populations using AI-guided formulation design, resulting in improved treatment outcomes and enhanced patient care Fig. 3 [114]. Studies by Lv et al. used DL to evaluate the phototoxic effect of Indocyanine Green-Chlorin e6 nanoparticles (ICG-Ce6 NPs) on in vitro-culture cancers in an effort to supersede time-consuming traditional and unreliable biochemical assays (live/dead staining method) for determining cell viability, which rely on the quality of the dye [115]. Lv and colleagues established a dataset of cells following PDT and trained the cell detection model YOLO v3 (You only look once), a real-time AI object detection algorithm, to quantify both the live and dead cells. This method demonstrated phenomenal abilities in cell detection, achieving mean precision (mAP) of 94 % and 71.3 % for live cells and dead cells, respectively. This method can effectively determine the efficacy of PDT treatment, thus expediting treatment development effectively. Studies by Maruyama et al. employed deep learning-based volumetric analysis to determine volumetric alterations of choroidal vessels following PDT and focal laser photocoagulation (PC) for central serous chorioretinopathy (CSCR) [116]. Maruyama and colleagues revealed that the 3-D volume of choroidal vessels and stroma was analysed using deep learning-based quantitative procedures at baseline and three months post-treatment. The results showed that PDT and focal PC reduced the vessel volume of the choroid in eyes with CSCR, suggesting that this algorithm may be essential for future pathological examination.

Overall, the incorporation of AI in drug delivery systems holds great promise for evolving formulation designs, forecasting drug characteristics, and optimising drug delivery performance. Through the utilisation of AI systems and large datasets, scientists can expedite the discovery of safe and efficacious drug delivery approaches, ultimately enhancing patient prognosis and advancing the field of PDD and PDT [115–117]. AI technologies can also determine optimal light distribution patterns as per patient-specific parameters, such as tissue architecture and tumour location [26]. Furthermore, AI can process imaging data and predict the optimal light delivery approach that allows for uniform illumination and efficient excitation of the PS retained in tumour tissues. AI algorithms can elucidate medical imaging data to

determine the appropriate dose required for efficient tumour treatment with minimal damage to surrounding healthy tissues [118]. Furthermore, AI algorithms can assist researchers with real-time treatment monitoring, enabling adjustments of light parameters based on the patient's response, which can also predict treatment outcomes. Yoo et al. designed a two-stage deep learning model to predict a 1-year outcome of PDT using initial multimodal clinical data. The training dataset entailed 166 eyes with chronic central serous chorioretinopathy (CSC) and an additional learning dataset comprising 745 healthy control eyes. Prior to being adjusted to predict CSC treatability using transfer learning, a pre-trained ResNet50-based convolutional neural network was trained with normal fundus photos (FPs) to identify CSC. The domain-specific ResNet50 effectively predicted susceptible and refractory CSC (accuracy, 83.9 %). Thereafter, XGBoost was used to integrate multimodal clinical data with the FP deep features. The final merged model (DeepPDT-Net), performed better than the domain-specific ResNet50 (accuracy: 88.0 %). Yoo and colleagues the DeepPDT-Net strategy, incorporating transfer learning and concatenating multimodal data, can circumvent the clinical prediction challenges arising from inadequate datasets [119].

AI offers tools that can improve the efficiency of PDT and PDD by optimising light distribution and dosimetry. AI technologies can customise treatment, allow for real-time modifications, and improve the overall therapeutic efficacy [24]. Liu et al. investigated the anticancer effects of a light-sensitive polymer nanocarrier encapsulating PS (RB-M) [120]. Liu and colleagues used an implantable wireless dual-wavelength microLED device capable of delivering two light wavelengths sequentially to programmatically regulate the release and excitation of the loaded PS. Two transmitter coils with corresponding resonant frequencies initiate the connected LEDs to emit varying wavelengths independently. Furthermore, an AI-based digital simulation device was used to determine optimal irradiation time, dose, and RB-M concentration. Liu et al. revealed that in vitro and vivo experiments exhibited significant inhibitory effects in an orthotopic rat liver hepatocellular carcinoma disease model, suggesting that a sequential low-dose light-mediated PDT strategy was efficacious at low PS and irradiation doses, which is a clinically significant event that enhances treatment safety. A study conducted by He et al. developed continuous AI-assisted DNA aneuploidy cytology (DNA-ICM) for monitoring dysplastic non-homogeneous dysplastic oral with moderate-to-severe dysplasia among the long-term follow-ups after treatment by 5-aminolevulinic acid-mediated PDT. DNA-ICM revealed 1 aneuploid cell 9 months following the initial session of PDT [121]. Following the second PDT session, the patient exhibited full respond to the treatment with DNA

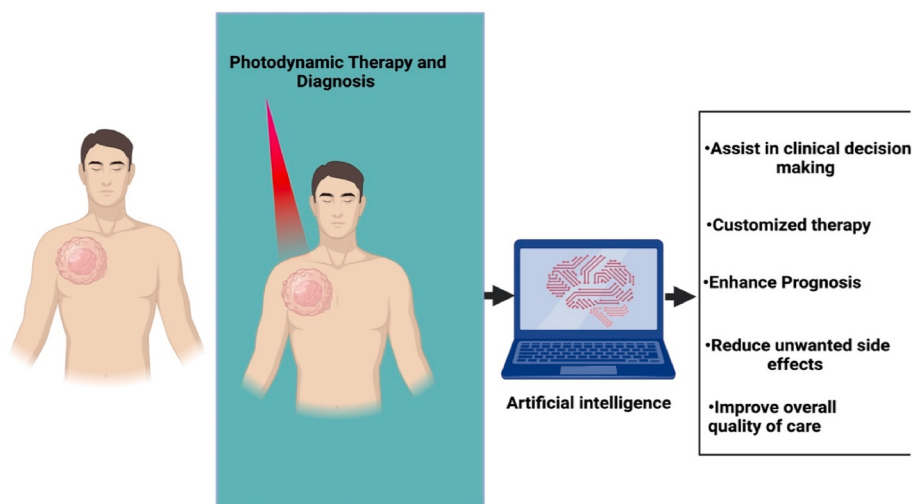


Fig. 3. AI systems for customising therapy and predicting treatment outcomes and prognosis in cancer patients.

ploidy. This type of research suggests that AI can efficiently evaluate the efficiency of PDT treatment, thus expediting up the discovery of new PSs.

9. Conclusion

In recent years, great strides have been made to improve the efficiency of PDT and PDD by integrating them with nanotechnology [46]. In addition to that, AI has shown great potential for further revolutionising drug delivery methods by promoting more accurate, customised, and effective therapeutic interventions. AI can effectively process large datasets, allowing for the development of personalised precision nanomedicine [122]. AI inputs in formulation design, molecular profiling, targeting approaches, drug release kinetics, and monitoring techniques hold great promise for enhancing diagnostic and treatment outcomes and patients quality of life. Furthermore, AI can optimise the developmental stages of nanomedicines by modifying their properties to achieve efficient drug synergy while minimising unwanted side effects [123]. This innovation ultimately improves the accuracy of treatment, customised dosing, and the overall performance of nanomedicines [86]. AI has the ability to forecast how nanocarriers will interact with their encapsulated agents, biological barriers, or cell membranes. AI algorithms can also estimate the drug encapsulation efficiency and design ideal drug release kinetics. These AI-based strategies can significantly optimise nanoformulations, enhancing the delivery of and targeting abilities of anticancer agents, including PSs, by helping researchers identify precise molecular targets for therapeutic interventions [124].

There are currently no real-time dosimetry equipment, thus clinicians forecast parameters for PS dose and light intensity to be supplied at the tissue interface, which have rarely yielded optimal light distribution in any patient [48]. Predicting light fluence within greater mass tissues is still remains an arduous task since analytic or computational techniques are needed to calculate the light fluence, together with accurate measurements of tissue absorption, scatter, and anisotropy factors [47]. Thus, without precise dosimetry, it becomes challenging to differentiate malfunctions caused by insufficient PS, light, or oxygen [48]. In this context, AI algorithms can help researchers monitor treatments in real-time by allowing them to modify light parameters in line with patient responses, which can also be used to forecast therapy outcomes. AI provides tools to optimise light distribution and dosimetry, increasing PDT and PDT efficiency [24]. In conclusion, AI has shown great potential in the fight against cancer. Desirable patient outcomes could be achieved from its integration in research, diagnosis, and treatment. However, ethical, regulatory, and data-related concerns may significantly impede the immediate implementation of AI in clinical settings. With ongoing investigation, collaboration, and modern technology, AI is poised to revolutionise future drug delivery strategies and pave new avenues for precision medicine.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work is based on the research supported by the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation of South Africa (Grant no. 98337).

Data availability statement

The authors confirm that the data supporting the results are available in this article. Additional data are available from the corresponding author, upon reasonable request.

CRediT authorship contribution statement

Nkune Williams Nkune: Writing – original draft, Conceptualization. Heidi Abrahamse: Writing – review & editing, Validation, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

- [1] F. Bray, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA A Cancer J. Clin.* (2024), <https://doi.org/10.3322/caac.21834>.
- [2] W. Park, et al., New opportunities for nanoparticles in cancer immunotherapy, *Biomater. Res.* (2018), <https://doi.org/10.1186/s40824-018-0133-y>.
- [3] I. Jovčevska, S. Muyldermans, The therapeutic potential of nanobodies, *BioDrugs* (2020), <https://doi.org/10.1007/s40259-019-00392-z>.
- [4] D.T. Debela, et al., New Approaches and Procedures for Cancer Treatment: Current Perspectives, *SAGE Open Medicine*, 2021, <https://doi.org/10.1177/20503121211034366>.
- [5] Z. Wang, et al., Application of Photodynamic Therapy in Cancer: Challenges and Advancements, *Biocell*, 2021, <https://doi.org/10.32604/biocell.2021.014439>.
- [6] A. Sharma, et al., Recent advancements in photodynamic therapy and cancer biosensor using natural products, *Talanta Open* (2023), <https://doi.org/10.1016/j.talo.2023.100261>.
- [7] S. Alexere, et al., A novel synthesis of a chlorophyll b-gold nanoconjugate used for enhancing photodynamic therapy: in vitro study, *Photodiagnosis Photodyn. Ther.* (2021), <https://doi.org/10.1016/j.pdpdt.2021.102444>.
- [8] S.M.I. Alexere, et al., Using biospeckle and LIBS techniques with artificial intelligence to monitor phthalocyanine-gold nanoconjugates as a new drug delivery mediator for in vivo PDT, *J. Photochem. Photobiol. Chem.* (2023), <https://doi.org/10.1016/j.jphotochem.2023.114687>.
- [9] N.W.N. Simelane, et al., Photodynamic diagnosis and photodynamic therapy of colorectal cancer in vitro and in vivo, *RSC Adv.* (2020), <https://doi.org/10.1039/D0RA08617G>.
- [10] M. Olszowy, et al., Current strategies in photodynamic therapy (PDT) and photodynamic diagnostics (PDD) and the future potential of nanotechnology in cancer treatment, *Pharmaceutics* (2023), <https://doi.org/10.3390/pharmaceutics15061712>.
- [11] D. Ho, et al., Artificial intelligence in nanomedicine, *Nanoscale Horizons* (2019), <https://doi.org/10.1039/C8NH00233A>.
- [12] J. Khong, et al., Chapter 22 - the role of artificial intelligence in scaling nanomedicine toward broad clinical impact, in: E.J. Chung, et al. (Eds.), *Nanoparticles for Biomedical Applications*, Elsevier, 2020, pp. 385–407.
- [13] N. Serov, V. Vinogradov, Artificial intelligence to bring nanomedicine to life, *Adv. Drug Deliv. Rev.* (2022), <https://doi.org/10.1016/j.addr.2022.114194>.
- [14] A. Stenzinger, et al., Artificial intelligence and pathology: from principles to practice and future applications in histomorphology and molecular profiling, *Semin. Cancer Biol.* (2022), <https://doi.org/10.1016/j.semcancer.2021.02.011>.
- [15] J. Elkhader, O. Elemento, Artificial intelligence in oncology: from bench to clinic, *Semin. Cancer Biol.* (2022), <https://doi.org/10.1016/j.semcancer.2021.04.013>.
- [16] H. Ding, et al., Preparation and application of pH-responsive drug delivery systems, *J. Contr. Release* (2022), <https://doi.org/10.1016/j.jconrel.2022.05.056>.
- [17] Z. Li, et al., Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency, *Adv. Sci.* (2022), <https://doi.org/10.1002/adv.202201734>.
- [18] X. Zheng, et al., A dendritic polymer-based nanosystem mediates drug penetration and irreversible endoplasmic reticulum stresses in tumor via neighboring effect, *Adv. Mater.* (2022), <https://doi.org/10.1002/adma.202201200>.
- [19] L. Luo, et al., GSH-sensitive polymeric prodrug: synthesis and loading with photosensitizers as nanoscale chemo-photodynamic anti-cancer nanomedicine, *Acta Pharm. Sin. B* (2022), <https://doi.org/10.1016/j.apsb.2021.05.003>.
- [20] J. Lipkova, et al., Artificial intelligence for multimodal data integration in oncology, *Cancer Cell* (2022), <https://doi.org/10.1016/j.ccell.2022.09.012>.
- [21] M. Kim, A. Darafsheh, Light sources and dosimetry techniques for photodynamic therapy, *Photochem. Photobiol.* (2020), <https://doi.org/10.1111/php.13219>.
- [22] H. Arabi, H. Zaidi, Applications of artificial intelligence and deep learning in molecular imaging and radiotherapy, *European J. Hybrid Imag.* (2020), <https://doi.org/10.1186/s41824-020-00086-8>.

- [23] H. Nosrati, M. Nosrati, Artificial intelligence in regenerative medicine: applications and implications, *Biomimetics* (2023), <https://doi.org/10.3390/biomimetics8050442>.
- [24] A.-A. Yassine, et al., Machine learning for real-time optical property recovery in interstitial photodynamic therapy: a stimulation-based study, *Biomed. Opt. Express* (2021), <https://doi.org/10.1364/BOE.431310>.
- [25] M. Mousavi, et al., Photodynamic therapy dosimetry using multiexcitation multiemission wavelength: toward real-time prediction of treatment outcome, *J. Biomed. Opt.* (2020), <https://doi.org/10.1117/1.JBO.25.6.063812>.
- [26] W.S. Kim, et al., AI-enabled, implantable, multichannel wireless telemetry for photodynamic therapy, *Nat. Commun.* (2022), <https://doi.org/10.1038/s41467-022-29878-1>.
- [27] S. Shahi, et al., Effect of Gelatinous Spongy Scaffold Containing Nano-Hydroxyapatite on the Induction of Odontogenic Activity of Dental Pulp Stem Cells, *Journal of King Saud University - Science*, 2022, <https://doi.org/10.1016/j.jksus.2022.102340>.
- [28] P. Salahshour, et al., Nanobiomaterials/bioinks based scaffolds in 3d bioprinting for tissue engineering and artificial human organ, *Advances in Biology & Earth Sciences* (2024), <https://doi.org/10.62476/abes9s97>.
- [29] N. Liu, et al., 3D bioprinted scaffolds for tissue repair and regeneration, *Frontier Mater.* (2022), <https://doi.org/10.3389/fmats.2022.925321>.
- [30] S. Kwiatkowski, et al., Photodynamic therapy – mechanisms, photosensitizers and combinations, *Biomed. Pharmacother.* (2018), <https://doi.org/10.1016/j.biopha.2018.07.049>.
- [31] J. Dobson, et al., Photodynamic therapy and diagnosis: principles and comparative aspects, *Vet. J.* (2018), <https://doi.org/10.1016/j.tvjl.2017.11.012>.
- [32] R.R. Allison, K. Moghissi, Photodynamic therapy (PDT): PDT mechanisms, *Clinical Endoscopy* (2013), <https://doi.org/10.5946/ce.2013.46.1.24>.
- [33] J. Zhang, et al., An updated overview on the development of new photosensitizers for anticancer photodynamic therapy, *Acta Pharm. Sin. B* (2018), <https://doi.org/10.1016/j.apsb.2017.09.003>.
- [34] D.K. Chatterjee, et al., Nanoparticles in photodynamic therapy: an emerging paradigm, *Adv. Drug Deliv. Rev.* (2008), <https://doi.org/10.1016/j.addr.2008.08.003>.
- [35] A. Nowak-Stepniowska, P. Pergol, A. Padzik-Graczyk, [Photodynamic method of cancer diagnosis and therapy—mechanisms and applications], *Postepy Biochem* 59 (1) (2013) 53–63.
- [36] H.-I. Kim, B.C. Wilson, Photodynamic diagnosis and therapy for peritoneal carcinomatosis from gastrointestinal cancers: status, opportunities, and challenges, *J. Gastric Cancer* (2020), <https://doi.org/10.5230/jgc.2020.20.e39>.
- [37] R.R. Allison, Fluorescence guided resection (FGR): a primer for oncology, *Photodiagnosis Photodyn. Ther.* (2016), <https://doi.org/10.1016/j.pdpdt.2015.11.008>.
- [38] B. Nokes, et al., Aminolevulinic acid (ALA): photodynamic detection and potential therapeutic applications, *J. Surg. Res.* (2013), <https://doi.org/10.1016/j.jss.2013.02.002>.
- [39] Hefti, M. et al. Fluorescence-Guided Surgery for Malignant Glioma: A Review on Aminolevulinic Acid Induced Protoporphyrin IX Photodynamic Diagnostic in Brain Tumors. *Current Med. Imag.* <https://doi.org/10.2174/157340510793205503>.
- [40] W. Stummer, et al., Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial, *Lancet Oncol.* (2006), [https://doi.org/10.1016/S1470-2045\(06\)70665-9](https://doi.org/10.1016/S1470-2045(06)70665-9).
- [41] I. Kausch, et al., Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies, *Eur. Urol.* (2010), <https://doi.org/10.1016/j.eururo.2009.11.041>.
- [42] G. Mowatt, et al., Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: systematic review and meta-analysis, *Int. J. Technol. Assess. Health Care* (2011), <https://doi.org/10.1017/S0266462310001364>.
- [43] I.S. Turan, et al., Molecular demultiplexer as a terminator automaton, *Nat. Commun.* (2018), <https://doi.org/10.1038/s41467-018-03259-z>.
- [44] A. Pulumati, et al., Technological advancements in cancer diagnostics: improvements and limitations, *Cancer Rep.* (2023), <https://doi.org/10.1002/cnr2.1764>.
- [45] S. Luo, et al., A review of NIR dyes in cancer targeting and imaging, *Biomaterials* (2011), <https://doi.org/10.1016/j.biomaterials.2011.06.024>.
- [46] O.C. Didamson Phd, H. Abrahamse, Targeted photodynamic diagnosis and therapy for esophageal cancer: potential role of functionalized nanomedicine, *Pharmaceutics* (2021), <https://doi.org/10.3390/pharmaceutics13111943>.
- [47] T. Hasan, et al., Photodynamic therapy dosimetry, in: *Holland-frei Cancer Medicine*, sixth ed., BC Decker, 2003.
- [48] R.R. Allison, et al., Photosensitizers in clinical PDT, *Photodiagnosis Photodyn. Ther.* (2004), [https://doi.org/10.1016/S1572-1000\(04\)00007-9](https://doi.org/10.1016/S1572-1000(04)00007-9).
- [49] D. Van Straten, et al., Oncologic photodynamic therapy: basic principles, current clinical status and future directions, *Cancers* (2017), <https://doi.org/10.3390/cancers9020019>.
- [50] G. Gunaydin, et al., Photodynamic therapy for the treatment and diagnosis of cancer—A review of the current clinical status, *Front. Chem.* (2021), <https://doi.org/10.3389/fchem.2021.686303>.
- [51] A.K. Jain, S. Thareja, In vitro and in vivo characterization of pharmaceutical nanocarriers used for drug delivery, *Artif. Cell Nanomed. Biotechnol.* (2019), <https://doi.org/10.1080/21691401.2018.1561457>.
- [52] N. Simelane, et al., Targeted nanoparticle photodynamic diagnosis and therapy of colorectal cancer, *Int. J. Mol. Sci.* (2021), <https://doi.org/10.3390/ijms22189779>.
- [53] A.M. Udrea, et al., Photosensitizers-loaded nanocarriers for enhancement of photodynamic therapy in melanoma treatment, *Pharmaceutics* (2023), <https://doi.org/10.3390/pharmaceutics15082124>.
- [54] M. Qasim, et al., Modulation of immune responses with nanoparticles and reduction of their immunotoxicity, *Biomater. Sci.* (2020), <https://doi.org/10.1039/C9BM01643K>.
- [55] J. Wu, The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application, *J. Personalized Med.* (2021), <https://doi.org/10.3390/jpm11080771>.
- [56] M.A. Subhan, et al., Recent advances in tumor targeting via EPR effect for cancer treatment, *J. Personalized Med.* (2021), <https://doi.org/10.3390/jpm11060571>.
- [57] X. Huang, et al., Targeted delivery and enhanced uptake of chemo-photodynamic nanomedicine for melanoma treatment, *Acta Biomater.* (2022), <https://doi.org/10.1016/j.actbio.2022.05.015>.
- [58] Z. Liao, et al., Smart nanocarriers for cancer treatment: clinical impact and safety, *NanoImpact* (2020), <https://doi.org/10.1016/j.nanoimp.2020.100253>.
- [59] E.J. Hong, et al., Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials, *Acta Pharm. Sin. B* (2016), <https://doi.org/10.1016/j.apsb.2016.01.007>.
- [60] M. Barani, et al., Nanodiagnosis and nanotreatment of colorectal cancer: an overview, *J. Nanoparticle Res.* (2021), <https://doi.org/10.1007/s11051-020-05129-6>.
- [61] D. Lombardo, et al., Smart nanoparticles for drug delivery application: development of versatile nanocarrier platforms in biotechnology and nanomedicine, *J. Nanomater.* (2019), <https://doi.org/10.1155/2019/3702518>.
- [62] J.B. Vines, et al., Gold nanoparticles for photothermal cancer therapy, *Front. Chem.* (2019), <https://doi.org/10.3389/fchem.2019.00167>.
- [63] T.K.L. Rezende, et al., Upconversion rare Earths nanomaterials applied to photodynamic therapy and bioimaging, *Front. Chem.* (2022), <https://doi.org/10.3389/fchem.2022.1035449>.
- [64] S. ho Hong, Y. Choi, Mesoporous silica-based nanoplateforms for the delivery of photodynamic therapy agents, *J. Pharmaceut. Investigat.* (2018), <https://doi.org/10.1007/s40005-017-0356-2>.
- [65] D. Singh, et al., Ceramic nanoparticles: recompense, cellular uptake and toxicity concerns, *Artif. Cell Nanomed. Biotechnol.* (2016), <https://doi.org/10.3109/21691401.2014.955106>.
- [66] J. Kaddkhoda, et al., Recent advances and trends in nanoparticles based photothermal and photodynamic therapy, *Photodiagnosis Photodyn. Ther.* (2022), <https://doi.org/10.1016/j.pdpdt.2021.102697>.
- [67] S. Tambunlerchai, et al., Skin penetration enhancement strategies used in the development of melanoma topical treatments, *AAPS J.* (2021), <https://doi.org/10.1208/s12248-020-00544-y>.
- [68] M. da Volta Soares, et al., Nanostructured delivery system for zinc phthalocyanine: preparation, characterization, and phototoxicity study against human lung adenocarcinoma A549 cells, *Int. J. Nanomed.* (2011), <https://doi.org/10.2147/IJN.S15860>.
- [69] S. Natesan, et al., Hypocrellin B and nano silver loaded polymeric nanoparticles: enhanced generation of singlet oxygen for improved photodynamic therapy, *Mater. Sci. Eng., C* (2017), <https://doi.org/10.1016/j.msec.2017.03.179>.
- [70] E.-H. Lee, et al., Chitosan-coated liposomes to stabilize and enhance transdermal delivery of indocyanine green for photodynamic therapy of melanoma, *Carbohydr. Polym.* (2019), <https://doi.org/10.1016/j.carbpol.2019.115143>.
- [71] D.B. da Silva, et al., Protoporphyrin IX (PpIX) loaded PLGA nanoparticles for topical Photodynamic Therapy of melanoma cells, *Photodiagnosis Photodyn. Ther.* (2021), <https://doi.org/10.1016/j.pdpdt.2021.102317>.
- [72] G. Chen, et al., Chitosan nanoparticles for oral photothermally enhanced photodynamic therapy of colon cancer, *Int. J. Pharm.* (2020), <https://doi.org/10.1016/j.ijpharm.2020.119763>.
- [73] P.G. Mahajan, et al., A potential mediator for photodynamic therapy based on silver nanoparticles functionalized with porphyrin, *J. Photochem. Photobiol. Chem.* (2019), <https://doi.org/10.1016/j.jphotochem.2019.03.034>.
- [74] D.J. Lee, et al., Photodynamic tumor therapy of nanoparticles with chlorin e6 sown in poly(ethylene glycol) forester, *J. Mater. Chem. B* (2015), <https://doi.org/10.1039/C5TB00414D>.
- [75] I. Oh, et al., Cancer cell-specific photoactivity of pheophorbide a-glycol chitosan nanoparticles for photodynamic therapy in tumor-bearing mice, *Biomaterials* (2013), <https://doi.org/10.1016/j.biomaterials.2013.05.017>.
- [76] F. Moret, G. Varchi, Drug delivery in photodynamic therapy, *Pharmaceutics* (2023), <https://doi.org/10.3390/pharmaceutics15071784>.
- [77] F. Alharbi, A. Vakanski, Machine learning methods for cancer classification using gene expression data: a review, *Bioengineering* (2023), <https://doi.org/10.3390/bioengineering10020173>.
- [78] A. Kawczyk-Krupka, et al., Photodynamic therapy in colorectal cancer treatment—the state of the art in preclinical research, *Photodiagnosis Photodyn. Ther.* (2016), <https://doi.org/10.1016/j.pdpdt.2015.07.175>.
- [79] A.A. Sebak, et al., Targeted photodynamic-induced singlet oxygen production by peptide-conjugated biodegradable nanoparticles for treatment of skin melanoma, *Photodiagnosis Photodyn. Ther.* (2018), <https://doi.org/10.1016/j.pdpdt.2018.05.017>.
- [80] M.L. Castilho, et al., Chlorin e6-EGF conjugated gold nanoparticles as a nanomedicine based therapeutic agent for triple negative breast cancer, *Photodiagnosis Photodyn. Ther.* (2021), <https://doi.org/10.1016/j.pdpdt.2021.102186>.
- [81] P. García Calavia, et al., Targeted photodynamic therapy of breast cancer cells using lactose-phthalocyanine functionalized gold nanoparticles, *J. Colloid Interface Sci.* (2018), <https://doi.org/10.1016/j.jcis.2017.10.030>.

- [82] J. Li, et al., Fluorinated-functionalized hyaluronic acid nanoparticles for enhanced photodynamic therapy of ocular choroidal melanoma by ameliorating hypoxia, *Carbohydr. Polym.* (2020), <https://doi.org/10.1016/j.carbpol.2020.116119>.
- [83] J.-E. Chang, et al., Hypocrellin B and paclitaxel-encapsulated hyaluronic acid-ceramide nanoparticles for targeted photodynamic therapy in lung cancer, *J. Photochem. Photobiol. B Biol.* (2016), <https://doi.org/10.1016/j.jphotobiol.2016.02.035>.
- [84] H.J. Hah, et al., Methylene blue-conjugated hydrogel nanoparticles and tumor-cell targeted photodynamic therapy, *Macromol. Biosci.* (2011), <https://doi.org/10.1002/mabi.201000231>.
- [85] B. Mao, et al., Cyclic cRGDFk peptide and Chlorin e6 functionalized silk fibroin nanoparticles for targeted drug delivery and photodynamic therapy, *Biomaterials* (2018), <https://doi.org/10.1016/j.biomaterials.2018.01.045>.
- [86] Weeraratna, I.N. et al. Artificial Intelligence Applications for Biomedical Cancer Research: A Review. *Cureus*. <https://doi.org/10.7759/cureus.48307>.
- [87] I.H. Sarker, Deep learning: a comprehensive overview on techniques, taxonomy, applications and research directions, *Sn Computer Science* (2021), <https://doi.org/10.1007/s42979-021-00815-1>.
- [88] M.J. Iqbal, et al., Clinical applications of artificial intelligence and machine learning in cancer diagnosis: looking into the future, *Cancer Cell Int.* (2021), <https://doi.org/10.1186/s12935-021-01981-1>.
- [89] S.S.F. Yip, et al., Impact of experimental design on PET radiomics in predicting somatic mutation status, *Eur. J. Radiol.* (2017), <https://doi.org/10.1016/j.ejrad.2017.10.009>.
- [90] M. Salehjahromi, et al., Comparison study of regularizations in spectral computed tomography reconstruction, *Sens. Imag.* (2018), <https://doi.org/10.1007/s11220-018-0200-4>.
- [91] S. Siddique, J.C.L. Chow, Gold nanoparticles for drug delivery and cancer therapy, *Appl. Sci.* (2020), <https://doi.org/10.3390/app10113824>.
- [92] Z. Zhang, E. Sejdici, Radiological images and machine learning: trends, perspectives, and prospects, *Comput. Biol. Med.* (2019), <https://doi.org/10.1016/j.combiomed.2019.02.017>.
- [93] Y. Xu, et al., Medical breast ultrasound image segmentation by machine learning, *Ultrasonics* (2019), <https://doi.org/10.1016/j.ultras.2018.07.006>.
- [94] M. Kawamura, et al., Revolutionizing radiation therapy: the role of AI in clinical practice, *J. Radiat. Res.* (2024), <https://doi.org/10.1093/jrr/rrad090>.
- [95] V. Grégoire, et al., Image guidance in radiation therapy for better cure of cancer, *Mol. Oncol.* (2020), <https://doi.org/10.1002/1878-0261.12751>.
- [96] J. Bajwa, et al., Artificial intelligence in healthcare: transforming the practice of medicine, *Future Healthcare J.* (2021), <https://doi.org/10.7861/fhj.2021-0095>.
- [97] M. Nishino, et al., Monitoring immune-checkpoint blockade: response evaluation and biomarker development, *Nat. Rev. Clin. Oncol.* (2017), <https://doi.org/10.1038/nrclinonc.2017.88>.
- [98] Y. Fu, et al., From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma, *J. Exp. Clin. Cancer Res.* (2019), <https://doi.org/10.1186/s13046-019-1396-4>.
- [99] A.H. Morrison, et al., Immunotherapy and prevention of pancreatic cancer, *Trend Cancer* (2018), <https://doi.org/10.1016/j.trecan.2018.04.001>.
- [100] Y. Yang, Cancer immunotherapy: harnessing the immune system to battle cancer, *J. Clin. Invest.* (2015), <https://doi.org/10.1172/JCI83871>.
- [101] Y. Zhang, Z. Zhang, The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications, *Cell. Mol. Immunol.* (2020), <https://doi.org/10.1038/s41423-020-0488-6>.
- [102] Y.R. Murciano-Goroff, et al., The future of cancer immunotherapy: microenvironment-targeting combinations, *Cell Res.* (2020), <https://doi.org/10.1038/s41422-020-0337-2>.
- [103] Z. Zhang, X. Wei, Artificial intelligence-assisted selection and efficacy prediction of antineoplastic strategies for precision cancer therapy, *Semin. Cancer Biol.* (2023), <https://doi.org/10.1016/j.semcancer.2023.02.005>.
- [104] B.K. Kashyap, et al., Smart nanomaterials in cancer theranostics: challenges and opportunities, *ACS Omega* (2023), <https://doi.org/10.1021/acsomega.2c07840>.
- [105] J.P. Abraham, et al., Clinical validation of a machine-learning-derived signature predictive of outcomes from first-line oxaliplatin-based chemotherapy in advanced colorectal cancer, *Clin. Cancer Res.* (2021), <https://doi.org/10.1158/1078-0432.CCR-20-3286>.
- [106] E. Farina, et al., An overview of artificial intelligence in oncology, *Future Sci. OA* (2022), <https://doi.org/10.2144/fsoa-2021-0074>.
- [107] A.A. Alexander-Bryant, et al., Bioengineering strategies for designing targeted cancer therapies, *Adv. Cancer Res.* (2013), <https://doi.org/10.1016/B978-0-12-407173-5.00002-9>.
- [108] S.A. Bustin, K.A. Jellinger, Advances in molecular medicine: unravelling disease complexity and pioneering precision healthcare, *Int. J. Mol. Sci.* (2023), <https://doi.org/10.3390/ijms241814168>.
- [109] V. Luţenco, et al., New horizons of artificial intelligence in medicine and surgery, *J. Clin. Med.* (2024), <https://doi.org/10.3390/jcm13092532>.
- [110] L. Cobiainchi, et al., Surgeons' perspectives on artificial intelligence to support clinical decision-making in trauma and emergency contexts: results from an international survey, *World J. Emerg. Surg.* (2023), <https://doi.org/10.1186/s13017-022-00467-3>.
- [111] P. Bannigan, et al., Machine learning directed drug formulation development, *Adv. Drug Deliv. Rev.* (2021), <https://doi.org/10.1016/j.addr.2021.05.016>.
- [112] A.A.K. Farizhandi, et al., Machine Learning Approach for Carrier Surface Design in Carrier-Based Dry Powder Inhalation, *Computers & Chemical Engineering*, 2021, <https://doi.org/10.1016/j.compchemeng.2021.107367>.
- [113] K.P. Das, C. J. Nanoparticles and convergence of artificial intelligence for targeted drug delivery for cancer therapy: current progress and challenges, *Front. Med. Technol.* (2023), <https://doi.org/10.3389/fmedt.2022.1067144>.
- [114] N.J. Schork, Artificial Intelligence and Personalized Medicine, *Cancer Treatment and Research*, 2019, https://doi.org/10.1007/978-3-030-16391-4_11.
- [115] S. Lv, et al., Efficient evaluation of photodynamic therapy on tumor based on deep learning, *Photodiagnosis Photodyn. Ther.* (2023), <https://doi.org/10.1016/j.pdpdt.2023.103658>.
- [116] K. Maruyama, et al., Deep learning-based choroidal volumetric analysis after photodynamic therapy or focal laser for central serous chorioretinopathy, *Invest. Ophthalmol. Vis. Sci.* 64 (8) (2023) 3366, 3366.
- [117] D. Ho, Artificial intelligence in cancer therapy, *Science* (2020), <https://doi.org/10.1126/science.aaz3023>.
- [118] C. Jiang, et al., Application and progress of artificial intelligence in radiation therapy dose prediction, *Clinic. Translat. Radiat. Oncol.* (2024), <https://doi.org/10.1016/j.ctro.2024.100792>.
- [119] T.K. Yoo, et al., DeepPDT-Net: predicting the outcome of photodynamic therapy for chronic central serous chorioretinopathy using two-stage multimodal transfer learning, *Sci. Rep.* (2022), <https://doi.org/10.1038/s41598-022-22984-6>.
- [120] J. Liu, et al., Wireless sequential dual light delivery for programmed PDT in vivo, *Light Sci. Appl.* (2024), <https://doi.org/10.1038/s41377-024-01437-x>.
- [121] M.-J. He, et al., Continuous artificial intelligence-assisted DNA aneuploidy cytology for surveilling dysplastic oral leukoplakia treated by photodynamic therapy, *Photodiagnosis Photodyn. Ther.* (2023), <https://doi.org/10.1016/j.pdpdt.2023.103588>.
- [122] H.Y. Yoon, et al., Engineering nanoparticle strategies for effective cancer immunotherapy, *Biomaterials* (2018), <https://doi.org/10.1016/j.biomaterials.2018.03.036>.
- [123] Z. Li, et al., A tumor cell membrane-coated self-amplified nanosystem as a nanovaccine to boost the therapeutic effect of anti-PD-L1 antibody, *Bioact. Mater.* (2023), <https://doi.org/10.1016/j.bioactmat.2022.08.028>.
- [124] O. Adir, et al., Integrating artificial intelligence and nanotechnology for precision cancer medicine, *Adv. Mater.* (2020), <https://doi.org/10.1002/adma.201901989> (Deerfield Beach, Fla.).